Appendages of Skin

Introduction

The appendages of skin are those of hard keratin—hair and nails—and of the glands—sebaceous, apocrine sweat, and eccrine sweat glands. Hair and nails are like skin. They have a stratum basale with stem cells, those stem cells produce keratinocytes that make keratin, and those keratinocytes degrade their nucleus and membrane-bound organelles to make room for more keratin, becoming corneocytes, terminally differentiated keratinocytes. Corneocytes are alive, have enzymatic activity, and maintain their desmosome connection to the other cells of the epithelium. Hair and nails are an epithelium—just like skin. The main difference between skin (**soft keratin**) and hair and nails, (**hard keratin**) is that hair and nails **don't make granules** (no stratum granulosum) and **don't desquamate**.

The common theme in skin appendages is that there is an invagination of the epidermis into the dermis. The epidermis, when not an appendage, has a stratum basale, spinosum, granulosum, and corneum. The corneum is the keratinized layer that is our skin. When there is an appendage, the epidermis invaginates. The epidermis is always anchored to a basement membrane that separates the epidermis (and the epidermal appendage) from the dermis. The invaginated epidermis is still squamous cells. The stratum basale divides into spinosum keratinocytes. But in the appendage there is no granulosum or corneum. Instead, the apical surface of the invaginated epidermis either becomes (as in glands) or terminates (as in nails or hair) at the lumen of the appendage, into which the hard keratin epithelium has grown. Being able to grasp this cellular, histological consistency makes learning the skin appendages that much easier.

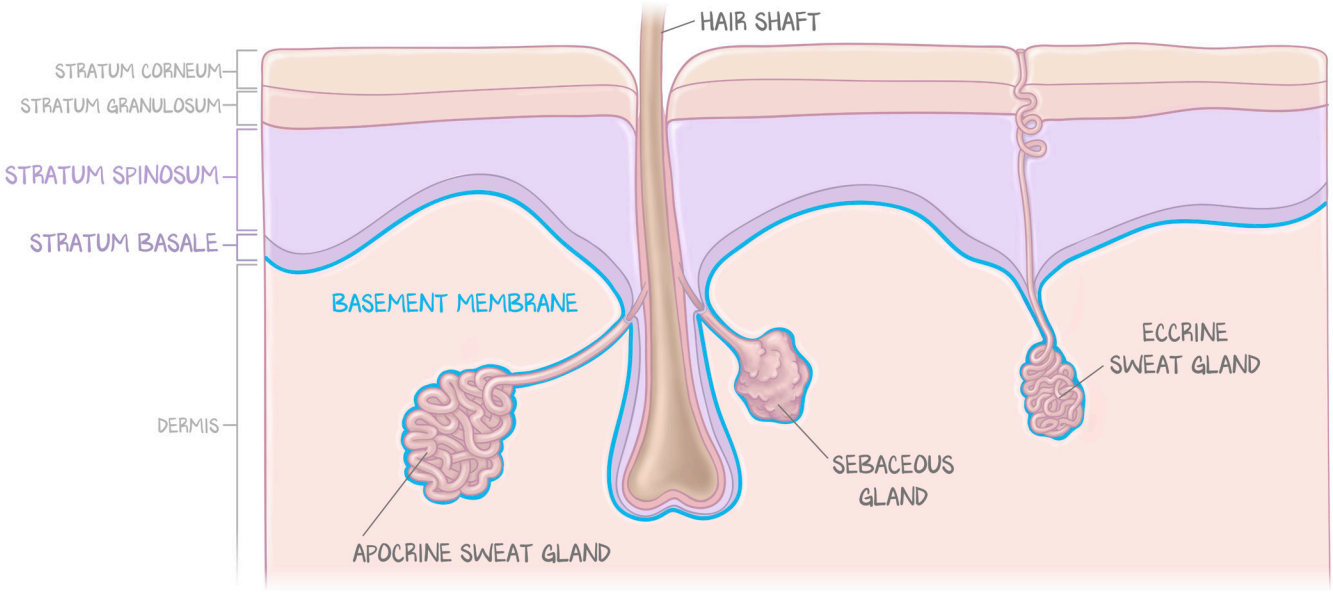

Figure 7.1: Appendages of Skin
This provides an overview for the majority of the lesson in which we discuss sweat glands, sebaceous glands, and hair. It is crucial to recognize that while these appendages can be seen in the same plane as the dermis, they are not dermal structures. they are in fact epidermal structures and share the basement membrane that separates the epidermis from the dermis. Eccrine sweat glands do their own thing while apocrine sweat glands, sebaceous glands, stem from the same hair follicle.

Hair and nails are keratinocytes that make hard keratin. Glands of the skin include those connected to hair follicles (apocrine and sebaceous glands) and those that exist on their own (eccrine) glands. We're going to cover a bunch of topics in this lesson. Hair anatomy, hair growth, and hair loss are first. Then we discuss the production of sebum in the context of acne. After acne, we cover sweating and the disorder of excess sweating called hyperhidrosis. Finally, we conclude with the physiology of nails and the nail bed.

Hair Anatomy

Perform this thought experiment. Visualize an epidermis-dermis junction at high magnification. You can see the epidermis from corneum to basement membrane. Remove the stratum corneum. A basement membrane separates the stratum basale from the dermis. There are melanocytes scattered throughout the stratum basale. Now, zoom out a little. See the enormous dermis capped by a tiny epidermis. There are rete ridges and dermal papillae. Now zoom so far out that you cannot see the individual cells anymore, just the layers—epidermis and dermis.

Visualize a hair follicle approaching the epidermis. This hair shaft is really long. At the bottom, there is a large bulbous structure from which the hair shaft originates. Drop that bulb onto your epidermis. The hair is heavy, so it pushes on the epidermis. The hair bulb sinks into the skin layer. As it progresses, it eventually gets deeper into the dermis. But as it does, it takes the epidermis with it. The hair follicle doesn't break the basement membrane, but rather drags the epithelium that is the epidermis deeper and deeper into the dermis. The hair follicle has its own concentric epithelium (the internal root sheath, discussed below) that is in contact with the concentric epidermal epithelium that is continuous with the epidermis of the rest of skin (the external root sheath). The hair follicle's epithelium (the internal root sheath) surrounds the hair shaft's epithelium (keratinized corneocytes). As this bulb invaginates the epidermis into the dermis, the epidermis epithelium folds on itself. The hair follicle and hair shaft are between the two layers of epidermis. The hair shaft counts as keratinized corneum, so these invaginated epidermis layers don't need to make their own. If you zoom back in on the invaginated epidermis you will see that there is no granulosum or corneum.

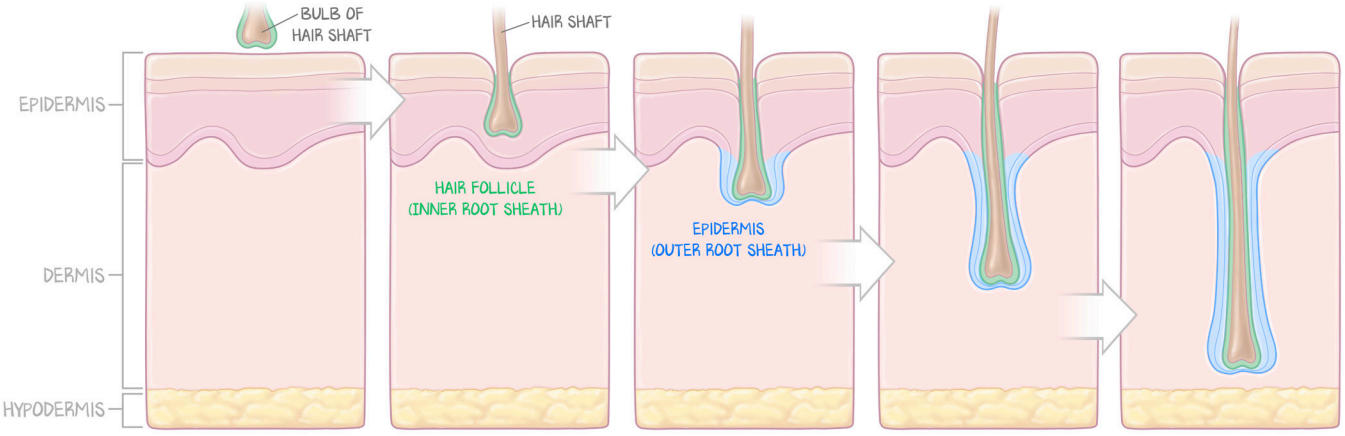

Figure 7.2: Hair Thought Exercise
The purpose of this illustration is to help you visualize the words around it. The details will unfold over the next few sections. Of course the hair grows from the bulb up the follicle and out into the air. But this exercise should reinforce that hair is an epidermal structure and set you up to master hair vocabulary.

The **hair follicle** describes the amalgamation of the glands, the hair shaft, the piloerector muscles, etc. It is the bulbous thing you visualized in the first paragraph. The epidermis surrounds the hair follicle as it invaginates deeper and deeper. The hair follicle is separated from the dermis by the epidermis and the epidermis's basement membrane. The hair follicle is all the stuff **beneath the skin**. The structure you are thinking of when you say "hair," the stuff you can run your fingers through on your own head, is the **hair shaft**. The hair shaft originates at the base of the hair follicle, and grows out to the skin surface through the hair follicle.

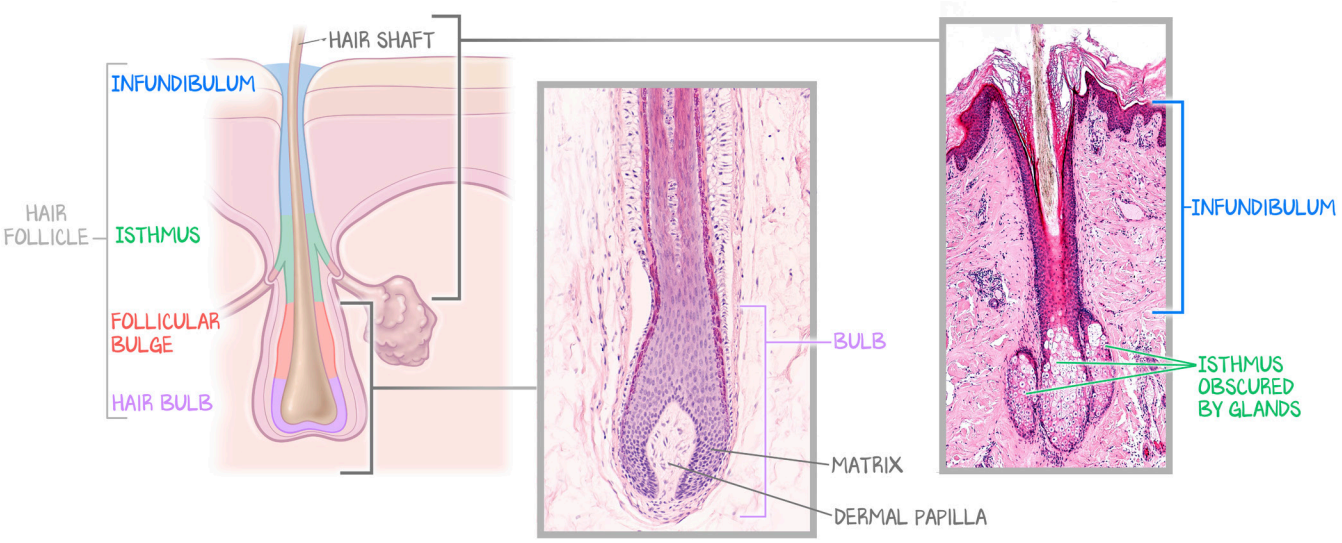

Figure 7.3: Segments of a Hair Follicle
(a) shows a low magnification histology preparation of a normal hair follicle with the regions of the corresponding segments color coded to the illustration in (b). The infundibulum is from the exit to skin to where the glands merge with the hair follicle. Where the glands connect to the hair follicle is the isthmus. The follicular bulge stores the stem cells which will replicate to grow the hair follicle during anagen and will apoptose to shrink the follicle during telogen. The hair bulb is the equivalent to the stratum basale of skin—stem cells replicate, melanocytes deposit pigment, and keratinocyte daughters enucleate to become corneocytes of the hair shaft. Like a dermal papilla, blood vessels are found at the root of the hair bulb.

The hair follicle has four continuous regions. The outermost region is the **infundibulum**, the common exit of the hair follicle, the hair shaft, and all associated glands. Each hair follicle is associated with a **piloerector muscle**. The **follicular bulge** is both where that piloerector muscle inserts onto the hair follicle and also where the **epidermal stem cells are** (the hair stem cells). More on this in a bit. The space between the infundibulum and the follicular bulge is named the **isthmus**, and is where sweat glands and sebaceous glands insert into the hair follicle. The deepest region of the hair follicle, deeper than the follicular bulge and its epidermal stem cells, is termed the **inferior segment**. This is where keratinocyte stem cells undergo rapid division and differentiation to become the epithelium of the hair shaft. Cell divisions happen in the inferior segment; epidermal stem cells are located in the follicular bulge.

The main structure of the inferior segment, the base of the hair follicle, is called the **bulb**. A dermal papilla wedges into the bulb. This dermal papilla provides the blood vessels that service the hair follicle. The bulb is where the keratinocytes of the hair shaft replicate.

Hair Histology

The hair shaft has an epithelium made of keratinocytes turned corneocytes with hard keratin. The hair follicle has an epithelium made of keratinocytes turned corneocytes with soft keratin. The epithelium of the hair follicle is termed the **internal root sheath**. The internal root sheath wraps around the hair shaft. The hair follicle is also surrounded by the epithelial layer of skin, the epidermis, continuous with and identical to the epidermis everywhere else. The epidermis, when it wraps around a hair follicle that has invaginated into dermis, is called the **outer root sheath**. The epidermis is separated from the dermis by a basement membrane, identical to and continuous with the epidermal basement membrane everywhere else. When that basement membrane separates the dermis from the epidermis around a hair follicle that has invaginated into dermis, that basement membrane is called a **glassy membrane**. What that means is that even though the hair follicle is at the level of dermis when assessed in two dimensions on a histology slide, the hair follicle is continuous with the air (like the epidermis of skin is) and is separated from the dermis by the epidermis. It isn't a dermal structure. It is an epidermal structure. It is its own layer on top of and separate from the epidermis layer.

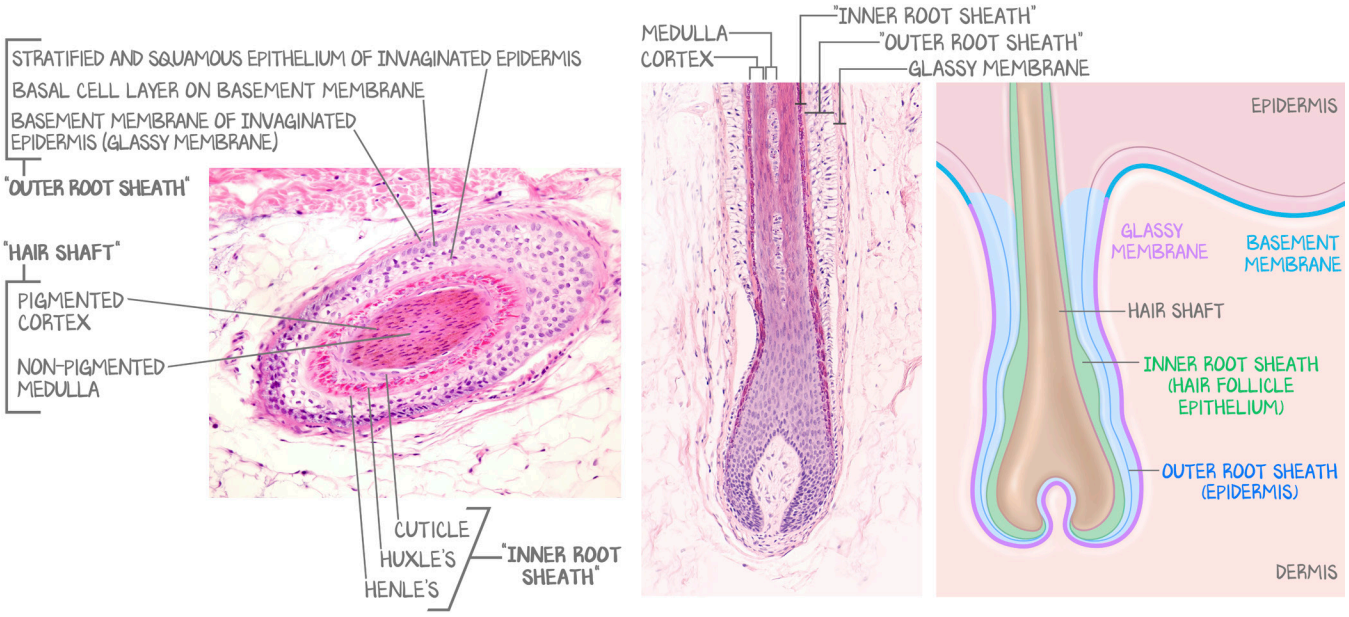

Figure 7.4: Histology of Hair
The hair shaft is what you think of as your hair. It is made of corneocytes and grows longer due to the proliferation of stem cells at the base of the bulb. Keratinocytes become the corneocytes of the hair shaft. The hair follicle epithelium, named the inner root sheath, is also made of corneocytes generated from the proliferation at the base of the bulb. The keratinocytes become corneocytes, but this layer does not continue past the isthmus, whereas the hair shaft does. The epidermis, now termed the outer root sheath, is the same epidermis you already know, except that it has no granulosum or corneum. This layer grows towards the hair follicle, perpendicular to the growth of the hair shaft and follicle. The epidermis (outer root sheath) is separated from the dermis by a basement membrane, which is continuous with the epidermis basement membrane and now called a glassy membrane.

The hair shaft and internal root sheath grow because new cells are added to the epithelium from the base of the hair follicle, from the bulb. This is also where the dermal papilla is, and thus where oxygen and nutrients are delivered via capillaries. As cells divide, they push the length of the hair follicle one cell layer up. The stem cells, the **epidermal stem cells**, must migrate from the follicular bulge down to the bulb. They migrate between the internal root sheath and the outer root sheath (the epidermis). When they arrive at the base of the hair shaft, they differentiate into **matrix cells**. Matrix cells are akin to hematopoietic blasts, which rapidly divide and differentiate into their cell line. Only here in the hair follicle, they divide and differentiate into keratinocytes. At the base of the bulb there are many nucleated keratinocytes all packed close together. There are also scattered melanocytes which provide pigment to keratinocytes. This region of the hair follicle is **highly pigmented** and has **densely packed**, **mitotically active** keratinocytes adjacent to an invagination of the dermal papilla.

Matrix cells proliferate and differentiate into keratinocytes. Those keratinocytes will differentiate into corneocytes. They differentiate into either keratinocytes that make soft keratin or keratinocytes that make hard keratin. The matrix cells will become **both** the keratinocytes of the hair shaft epithelium as well as the cells of the internal root sheath epithelium. The cuticle layer of the hair shaft is contiguous with the cuticle layer of the hair follicle. This provides a strong anchor that prevents the hair shaft from simply falling out as it gets too long. And yet these are two, separate, distinct epithelia. The internal root sheath epithelium ends at the isthmus, where the glands of the ducts connect to the hair follicle. The hair shaft epithelium continues until the very end of each strand of hair.

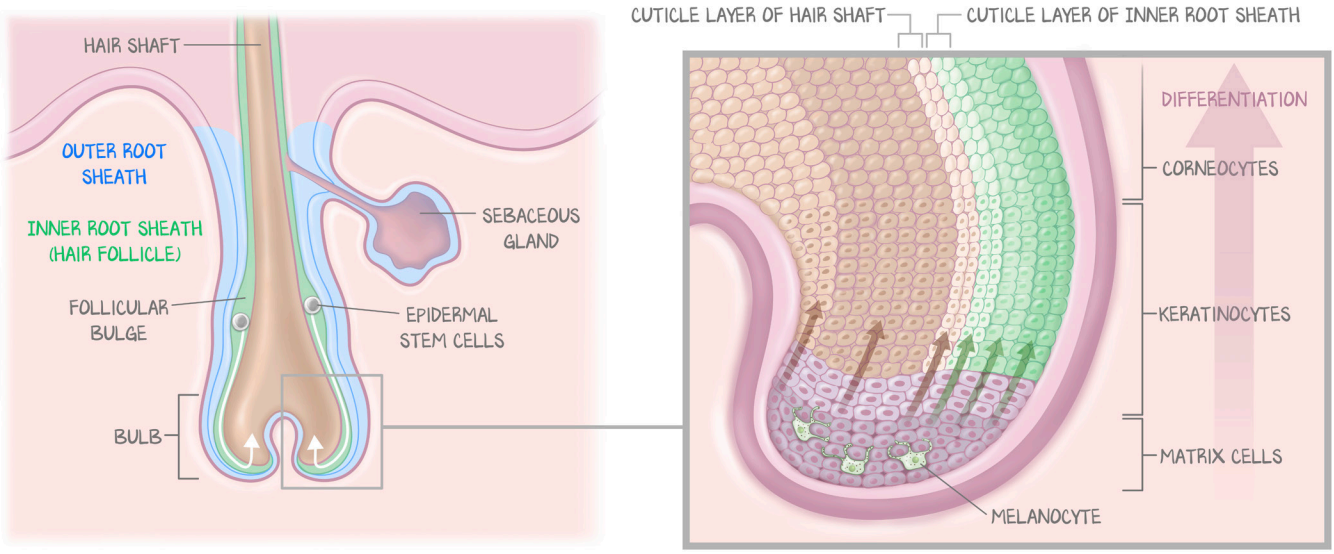

Figure 7.5: Elongation of Hair
The details of how proliferation at the bulb contributes to the medulla, cuticle, and hair follicle epithelium. From the follicular bulge epidermal stem cells become matrix cells at the base of the bulb. There they replicate. Melanocytes provide pigment. There is a progressive change in cell behavior from the center of the hair shaft out towards the hair follicle epithelium. All start as kertainocytes and all become corneocytes. The corneocytes of the medulla are tightly packed and give hair its strength. The cuticle of the hair shaft is continuous with cuticle of the hair follicle epithelium. The hair shaft cuticle will let go (sever desmosomes) from the epithelum of the hair follicle. the cuticle remains attached to the hair shaft.

The hair shaft epithelium can be divided into three concentric zones—the medulla, the cortex, and the cuticle. The **medulla** is the innermost layer. It is made of keratinocytes with soft keratin. The medulla does not extend outside of the hair follicle, and so will not be present if you analyze the histology of a hair shaft that was cut at the hair salon. The **cortex** is the middle layer of the hair shaft. It accounts for 80% of the hair shaft. It is the hard keratin. It is many, many cells thick. The **cuticle** is small cell layer on the outside of the hair shaft, surrounding the cortex. The cuticle is only a few layers thick. The keratinocytes of this layer produce soft keratin. They act as a divider, separating the main epithelium of the hair shaft (the cortex, hard keratin) from the epithelium that is the internal root sheath (corneocytes, soft keratin). The corneocytes of the hair shaft (the cortex corneocytes and the cuticle corneocytes) are connected to each other by desmosomes. The outermost corneocytes of the hair shaft produce soft keratin. There is no basement membrane between the cuticle and the internal sheath epithelium. There are also no connections, no desmosomes, between the soft keratin-producing corneocytes of the cuticle and the soft-keratin-producing corneocytes of the internal sheath.

The internal root sheath epithelium also has three layers: a cuticle confluent with the cuticle of the hair shaft and then two other layers named after people. The eponymous layers don't matter, so we suggest you learn it only as "internal root sheath" and cleave off excess details. On one side, the internal root sheath epithelium (corneocytes, cuticle) are confluent with the hair shaft epithelium (corneocytes, cuticle). On the other side, the internal root sheath epithelium is in contact with but not connected to the external root sheath. The external root sheath is epidermis, epidermis without a stratum granulosum or stratum corneum.

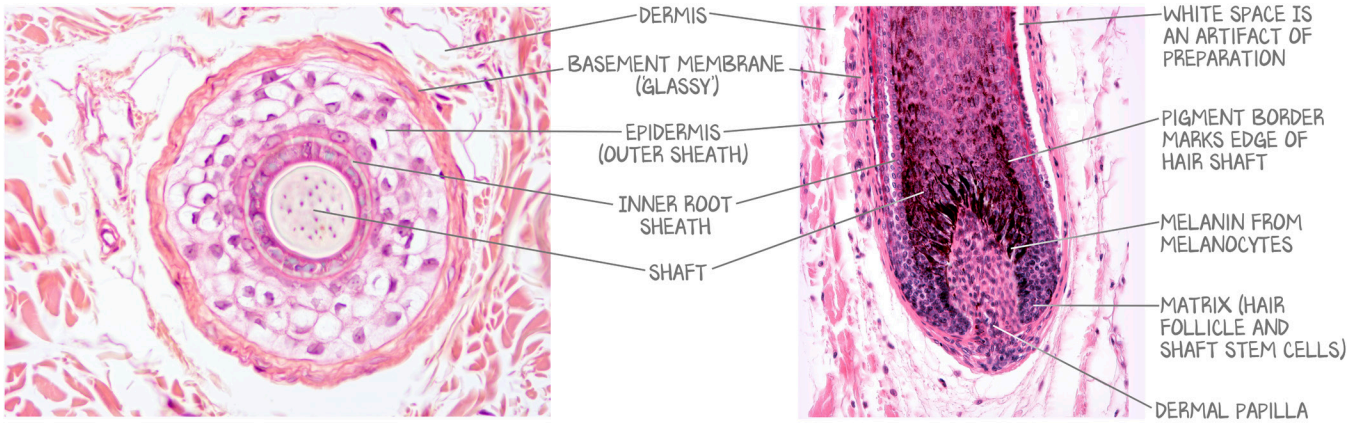

Figure 7.6: Hair Histology Magnified
The axial section on the left shows the relative size of the layers and hair shaft closer to the isthmus, as most of the keratinocytes have shrunken in size, ejected their nuclei (some blue dots persist in the medulla in this section), and terminally differentiated into corneocytes. The longitudinal section to the right shows a hair follicle near the bulb. Here, the keratinocytes are still nucleated and have grown in size from their stem cell niche in the matrix. They also receive pigment from melanocytes. Although the matrix forms both the inner root sheath and the hair shaft, it is clear where the hair shaft ends and the outer sheath begins. Only the hair shaft has pigment. Be careful, despite the numerous nuclei (blue dots) in the dermal papilla, these are cells of the dermis, of the blood vessels that supply the hair bulb. The matrix cells (purple with darker nuclei) are clearly distinct from the cells of the dermal papilla (pink with darker nuclei).

As the hair shaft exits the hair follicle, as it rises above the skin, both the cuticle layer and the cortex layer continue to the end of the strand of hair they are part of. The cortex constitutes the major part of the mass of the human hair, and it is formed by elongated, fusiform cells and long proteins that twist like the curly cord on a telephone. Try stretching a hair and you'll find that it's elastic—it stretches before it breaks. When you stretch a hair, you are straightening the coiled proteins in the cortex. When you release the hair, the proteins coil up again. The cuticle protects the cortex. The cuticle cells are arranged like scales of a fish or shingles on a roof, their free edges oriented away from the cortex. Cuticle keratinocytes are **not pigmented**, so appear translucent. Cuticle keratinocytes act as a barrier, protecting the cortex. The cortex keratinocytes are **pigmented** and supply those proteins that give hair its shape and strength.

By the time a keratinocyte has reached the end of the lower third of the hair follicle, the keratinocyte has already terminally differentiated into a corneocyte, having lost its nuclei and membrane-bound organelles. That means that there should be no nuclei visible in the hair shaft for the majority of the length the hair shaft is in the hair follicle. These corneocytes, like those of the skin, are **not dead**. They might as well be, given that they have no metabolic activity. Which is a good thing, too, because there aren't capillaries at the ends of your hair, only at the base at the bulb of the hair follicle. But these cells are neither apoptotic nor necrotic. They are merely **terminally differentiated**. Before they lose their nuclei, they make keratin, just as the keratinocytes of the epidermis do. But the keratin made by the keratinocytes of the hair shaft epithelium is different from the keratin of skin, in that it has abundant sulfur. The keratin, keratin-associated proteins, and the abundant sulfur are how this keratin is firm, and different from the keratin of skin.

Hair Growth Cycles

All skin has hair except for the palms, soles, glans penis, labia minora, and the clitoris. The dark hair visible with the human eye is called **terminal hair**. The hair that is everywhere else, that which is not seen by the naked eye, is called **vellus hair**. Balding is the loss of production of terminal hair, which is replaced with vellus hair. The skin still has hair on it, but that hair cannot be seen, does not get long, and is not deeply keratinized.

There are three phases of hair growth: anagen, catagen, and telogen. It is a cycle. We choose to start the cycle's story at the end of telogen, at the beginning of anagen.

Anagen begins. At the beginning of anagen, there is no bulb. The follicular bulge houses the stem cells. After having regressed in phases two and three, the hair follicle at the start of anagen can be as small as one-third its maximum anagen size. Cellular replication begins within the follicular bulge. This replication of cells takes up space, increasing the size of the hair follicle. The follicle elongates, invaginating into the dermis and hypodermis. The cells that will become the stem cells of keratinocytes for the hair shaft come from the replication of the cells at of the follicular bulge and become the cells at the basal layer of the bulb. The hair shaft begins to grow up from the bulb, keratinocytes to corneocytes who make hard keratin. The hair shaft grows out of the follicle and out of skin, visible now above skin. The bulb is continuously undergoing divisions. Hair will grow out from the bulb until anagen ends. Anagen, for hairs on the scalp, lasts years. The capillaries at the dermal papilla supply the metabolically active keratinocyte stem cells with oxygen and glucose to sustain their rapid proliferation. This is also why chemotherapy causes hair to fall out. Any follicle in anagen is poisoned by the chemotherapy (which targets actively replicating cells). The interruption of the stem cell proliferation causes the epithelium of the hair shaft to lose its continuous cellular connection to newly growing corneocytes. The shaft, no longer tethered to the follicle, falls out. At the end of anagen is the start of catagen.

In **catagen**, the keratinocytes within the bulb are still actively replicating, but the hair follicle begins to regress. The hair shaft continues to extend in length, but the follicle itself returns to its pre-anagen size. Regression is mediated by apoptosis of the cells of the hair follicle epithelium—those that replicated from the follicular bulge to grow the hair shaft now apoptose to return it to their original size. Catagen lasts for several weeks as the cells apoptose and the follicle shrinks.

In **telogen**, the follicle has already regressed to the original pre-anagen size, and now the bulb stops replicating as well. Telogen can last for as little as a week (arm hair) to almost a year (scalp hair). Hairs in telogen are prone to **shedding**, and this is what you brush away or what falls out when you shower. At the end of telogen, anagen begins anew.

During the catagen stage, the epithelial cells at the base of the follicle undergo apoptosis, whereas the dermal papilla remains intact. It is pulled upward by the apoptosis until it comes to rest next to the stem cells of the hair follicle bulge. This situation persists during the telogen stage. In anagen, the cells at the base of the follicle—the follicular bulge—proliferate. As new cells are generated from the follicular bulge stem cells, the addition of cells pushes those that were already present downward—the downward growth of the follicle envelops the dermal papilla once again.

Sweat Glands

Both apocrine sweat glands and eccrine sweat glands have a similar structure and physiology. Let's hit on the overall concept then explore each in detail.

All sweat gland epithelium is continuous with the epithelium of the epidermis. All sweat glands share the same continuous basement membrane to the epidermis. Like hair follicles, even though the main part of the gland, the secretory component, is located at the level of the dermis on 2D section, **sweat glands are epidermal structures**. They are invaginations of the epidermis with terminal differentiation of basal cells into gland cells. All sweat glands have a secretory component and a duct component. The **secretory component** consists of **secretory cells** and is surrounded by **myoepithelial cells**. Secretory cells make the stuff; myoepithelial cells ensure that the stuff is moved toward the skin surface. The **duct** segment is lined by an epithelium that is only one cell thick. The ducts are tubules, and, like the tubules of the nephron, the tubules **resorb**.

Apocrine sweat glands are **connected to hair follicles**. Apocrine glands are few in number (100,000) have a large diameter (2–3 mm). They are located in the **axillary** and **anogenital** regions only, and are not about regulation of temperature. These are the glands that make you smell bad and why there is a deodorant industry. They produce **pheromones** as well as a carbohydrate- and lipid-rich secretion. We don't know what these glands are for. The secretion itself doesn't smell bad, but the bacteria on your skin that consume the secretion do. This is why there are two separate products for underarm treatment—antiperspirants reduce fluid secretion, and deodorants mess up the bacteria that make you smell bad.

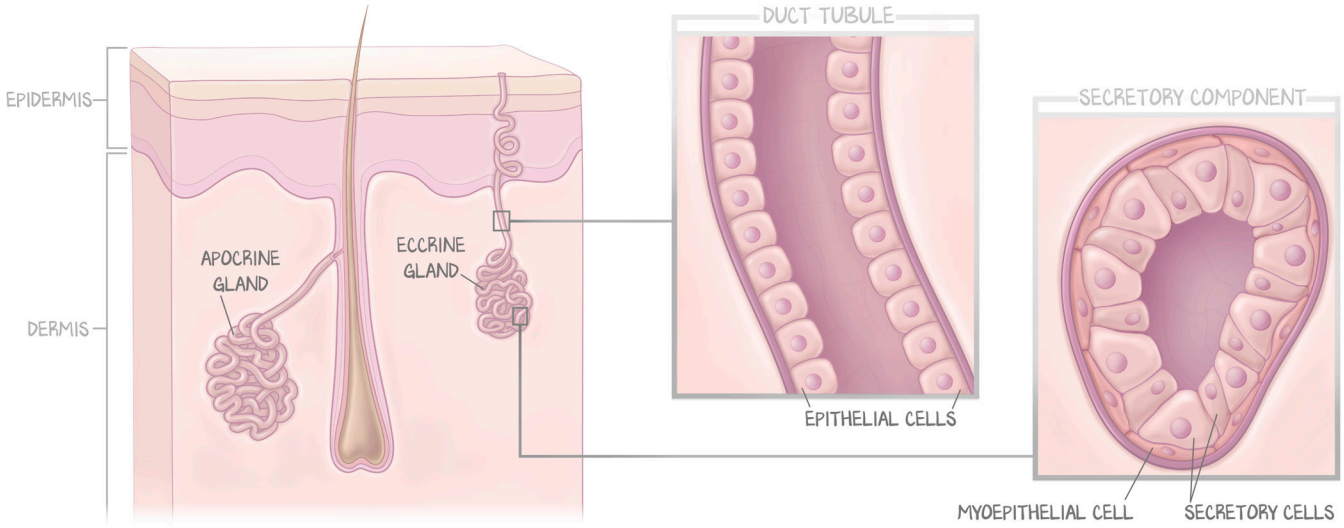

Figure 7.7: Sweat Glands
Apocrine sweat glands connect to the hair follicle. Eccrine sweat glands connect to the skin surface. The tubular nest in dermis (though separated from dermis by the basement membrane of the epidermis)are full of secretory cells. These generate the fluid that generates secretions. The ducts through the dermis are straight, then coil throughout the epidermis, emerging on the skin surface.

Eccrine sweat glands are **NOT connected to hair follicles** but represent a similar concept of epidermal invagination and differentiation into the dermis. Eccrine glands are many in number (millions) and are very small in diameter (50–100 μm). They are numerous on the palms and soles. Eccrine glands do not make you smell bad. They make you wet so you can cool off. Eccrine glands are innervated by **cholinergic** neurons of the **parasympathetic system**. The secretory cells are called **coiled cells** because the gland assumes the shape of a coil. Coiled cells are stimulated via M2 acetylcholine receptors, which induce the IP_3-DAG-Ca^{++} intracellular pathway, and secrete an isotonic fluid into the ducts. The ducts travel up to the epidermis, where the epidermis assumes the role of the duct. Along the way, the duct cells **resorb solute** but are relatively **impermeable to water**. This means that the final sweat product is always **hypotonic**.

In the acinus, the secretory component of the gland, a **basolateral sodium-potassium-dichloride** channel brings sodium down its concentration gradient to move potassium and chloride up their concentration gradients. You saw this channel in Renal Kidney #4: *Regional Transport and Pharmacology*, only now it's on the basolateral membrane. Once in the cell, chloride wants out of the cell, wants to move down its concentration gradient. In the apical membrane, which feeds the lumen of the gland, there is a chloride leak channel. This moves a negative charge into the lumen. To balance the electric charge, sodium moves paracellularly into the lumen. Because the epithelium is permeable to water, water follows salt into the lumen. Chloride is actively pumped into the cell, which requires ATP to establish and maintain a favorable sodium concentration. The rest is all passive, Na moving to balance the charge, water moving to balance osmolarity. The result is a **protein-free filtrate** that is **isotonic** to blood.

In the duct, **ENaC channels** allow sodium to be resorbed, down sodium's concentration gradient. This is passive. In the duct, **CFTR chloride** (cystic fibrosis transmembrane-conductance regulator) channels bring chloride up its concentration gradient. This epithelium is impermeable to water. The result of removing ions but leaving water is the **hypotonic** secretion of fluid. In the disease cystic fibrosis, caused by a defect of the CFTR gene, the genetic defect results in really salty sweat—the inability to resorb chloride creates an electrochemical force that keeps sodium in the lumen.

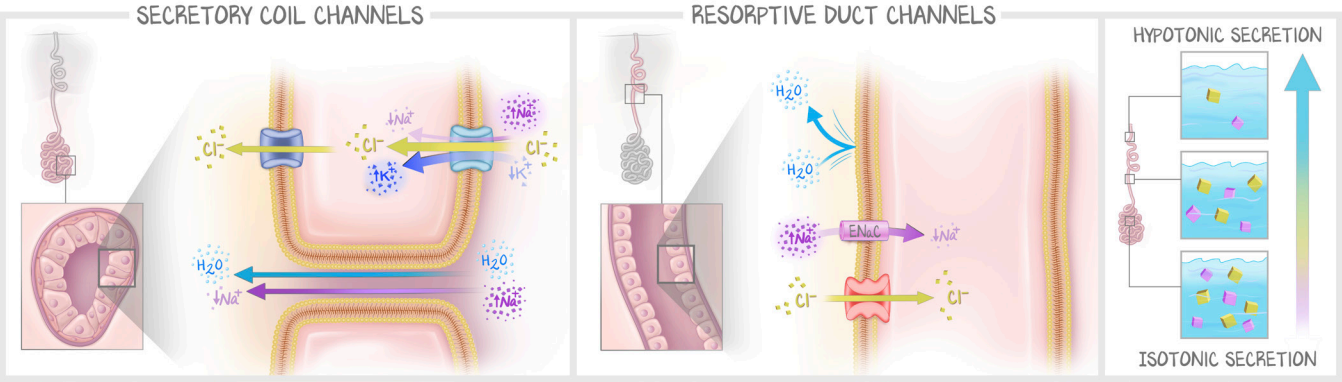

Figure 7.8: Channels in Coil Ductal Cells
Eccrine sweat glands release chloride into the ducts in the coiled segment. This causes paracellular movement of sodium and with it water. An isotonic tubule fluid is thus produced. As the fluid passes up the ducts to the skin surface, chloride is actively pumped out of the tubule and into the cell. ENaC channels (the same as the collecting duct and under the influence of aldosterone) resorb sodium, the sodium following the chloride once again. The membrane is impermeable to water. Solute is removed from the duct but water not, thus the sweat that is produced is hypotonic.

Sebaceous Glands

As we saw with the epidermis invagination ending with the hair follicle, some of the keratinocytes of the stratum basale can be induced to become sebaceous gland cells. Sebaceous glands have a basal cell layer, those basal cells are attached to the same basement membrane of the epidermis, and those basal cells divide and differentiate a daughter into a keratinocyte, just like the epidermis. Well, sort of. But see the parallels—the sebaceous gland epithelium is continuous with and works very similar to the epidermis epithelium. The sebaceous gland cells will eventually terminally differentiate, enucleate and eject their organelles, and be filled with a substance, just like keratinocytes. The sebaceous gland cells are held together by desmosomes and eventually "desquamate" like keratinocytes. The difference is that sebaceous gland cells are filled with a lipid product called **sebum** and they "desquamate" into the pilosebaceous canal, where the hair shaft is.

Like apocrine sweat glands, sebaceous glands are actively stimulated during puberty. The purpose of sebum is unclear. But the consequence of sebum production is quite clear, and is why teenagers have so much difficulty with **acne**. Quite the opposite of clear skin.

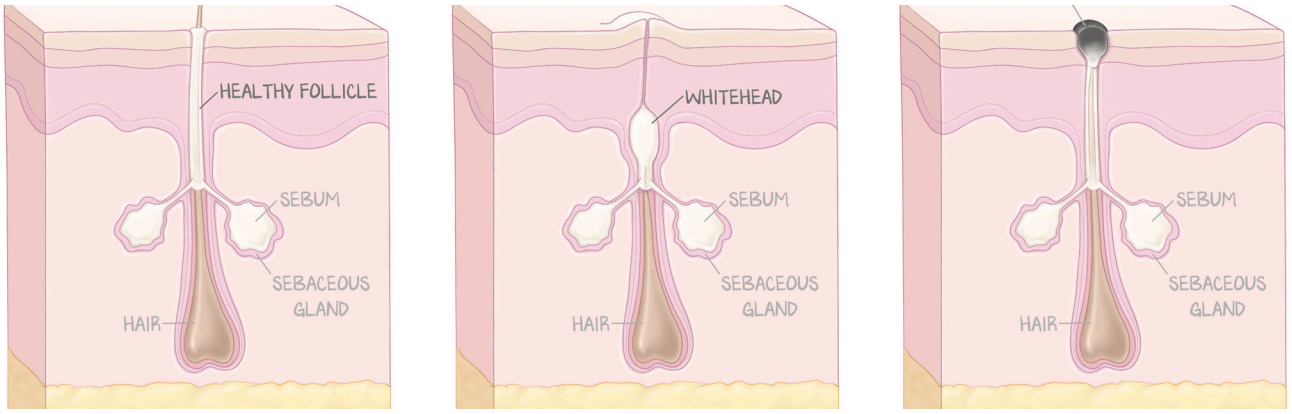

Figure 7.9: Pilosebaceous Canal
We are uncertain of sebum's intended physiologic role. But we know it is secreted into the hair follicle and coats the hair shaft. When too much gets produced it sets up a nidus for infection. If an obstruction/infection happens deep in the hair follicle, no oxygen can get to the sebum and the lesion is raised—a whitehead. If the obstruction/infection occurs close to the surface, oxygen oxidizes the lesion and it turns dark in color—a blackhead.

Acne

Sebaceous glands are found in hair-covered areas, where they are connected to hair **follicles**. The structure consisting of hair, hair follicle, arrector pili muscle, and sebaceous gland is an epidermal invagination known as a **pilosebaceous** unit. Acne happens when the **pilosebaceous unit becomes occluded**. When a follicle becomes **hyperkeratinized**, it blocks up the outflow track of the pilosebaceous unit. When the pilosebaceous unit is blocked up, it is called a **comedo** (plural comedones). Combine that with **excess sebum production** from the sebaceous glands (such as during puberty when there is excess androgen), and you end up with a whole lot of gunk in that comedo. P. acnes lives on the skin, and loves to find a comedo. Inside the "skingloo," *P. acnes* is protected from oxidizing air and feeds on the excess sebum, which it converts into **pro-inflammatory fatty acids**. Blocked pores, pro-inflammatory acids, and infection lead to the syndrome of acne.

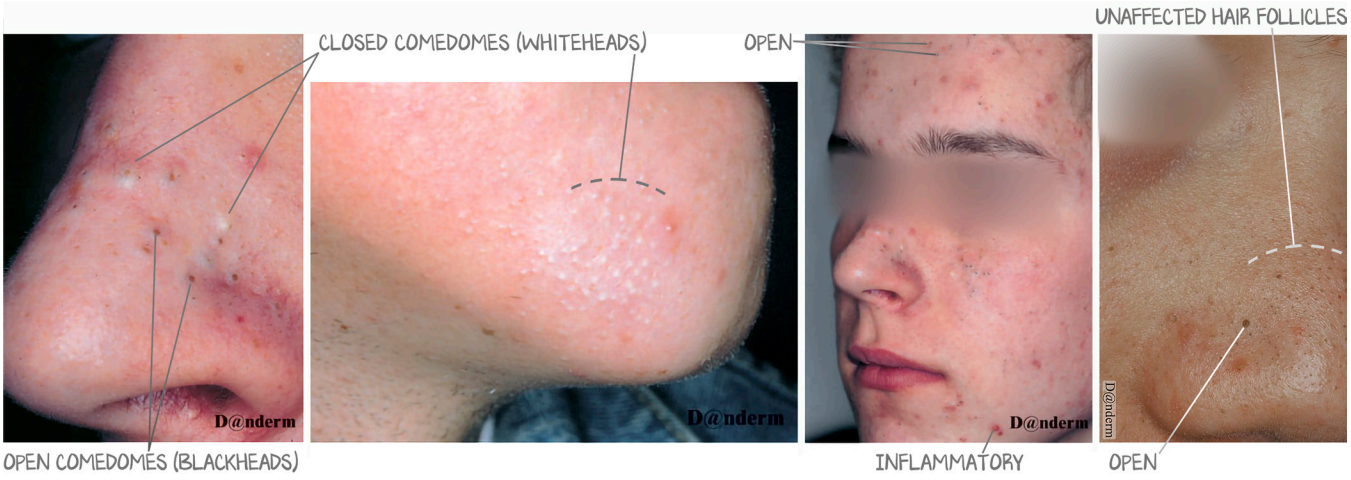

Figure 7.10: Acne
Closed comedones are whiteheads, and open comedones are blackheads. When acne causes redness, irritation, and inflammation, it is considered inflammatory. Everyone who has reached this stage in their career knows what acne is—you either had it, were grossed out by it, or made fun of someone who had it (it's called being a teenager). And although it's not a life-threatening illness, it can be disfiguring due to scarring, and it does matter a lot to a child developing into an adult.

Acne's appearance varies by its type. There are two kinds of **noninflammatory comedones**—whiteheads and blackheads. **Blackheads** (or open comedones) appear as dark brown/black "dots" at the surface of the pore. They are black because they are close enough to the pore surface for air to oxidize the sebum. **Whiteheads** (or closed comedones) are small, 1–2 mm "bumps" in the skin. Whiteheads are located deeper in the pore with only a microscopic opening to the skin surface. Being unexposed to oxygen, they do not change color. Being deeper, they push more skin out. **Inflammatory comedones** are erythematous, angry, and can appear as papules or pustules.

Rosacea

Rosacea is a poorly understood inflammatory disease. A picture of rosacea, a still image without context, can look like acne, but has nothing to do with bacteria or comedones. Rosacea presents as easy flushing, **erythema**, with **telangiectasias**, and superimposed **papules and pustules.** There will be **no comedones**. But while it can look like really bad acne, rosacea is more of an acute issue, erupting when exposed to external stimuli (**alcohol, sunlight, heat, spicy foods, stress**), and is unrelated to hormones. There are two sneaky tidbits about rosacea—**rhinophyma** (bulbous deformation of the nose) with phymatous rosacea, and **ocular manifestations** on the eyelids. Usually, rosacea is just some red splotchies after emotional stress. The test likes to give you the severe form, because it could be acne when written as a vignette.

Nails

Nails are analogous to hair in that nails are made of corneocytes that have hard keratin, the hard keratin is generated from a matrix at its proximal origination in the epidermis, and the epidermis where the nail is has no corneum or granulosum. It's why we spent so much time on hair. The nail fold is similar to the hair follicle bulb. The nail bed is similar to the epidermis that surrounds the hair follicle. The nail plate, the sheet of corneocytes with hard keratin, is similar to the hair shaft.

The **nail bed** is epidermis, just like all the epidermis near it. Except there is a linear invagination of that epidermis into the dermis. Unlike the glands and hair follicles, which are cylindrical and so generate a tubule through which epithelia run, this invagination is linear and shallow. This causes the epidermis to fold over itself. Where that overlap occurs is called the **nail fold**. Within the nail fold can be found the dorsal matrix, which contributes keratinocytes to the formation of the nail plate from the top, and the ventral matrix, which contributes keratinocytes to the formation of the nail from underneath. Matrix cells are keratinocytes birthed from the stratum basale, just like skin. Matrix cells turn into hard keratin, just like the hair shaft. Keratinocytes build hard keratin, don't use keratin granules, then differentiate into corneocytes, just like the hair shaft. And just like the corneocytes of the hair follicle, nail cells do not desquamate.

These cells form the **nail plate**, the thing you see when you look at your fingers, the thing you would have just called "the nail." That nail plate is firmly adhered to the fingertip. The plate is growing out from the nail fold, but is riding on epidermis below the nail plate, the nail bed. The nail bed is specialized epidermis that does not have a stratum granulosum or stratum corneum. Look at your right index finger, pointed to your left. You intuitively know that the nail "grows out" to the left, right? But think about the layer of skin UNDER the nail. That layer is "growing up" and should lift the nail up. But it doesn't. It doesn't because under the nail is the nail bed, and the stratum spinosum goes right up to the nail plate. If you ever have your nail ripped off, underneath isn't thick skin like the back of your hand. It appears more like an erosion or ulcer because there is no corneum underneath. But there has to be a histologic transition from nail bed (no corneum, no granulosum) to regular skin (yes granulosum, yes corneum). Those transitions occur at the free edge of the nail (**hyponychium**) and at the proximal nail fold (**eponychium**). It also occurs at the lateral nail folds, but we don't give them a special name.

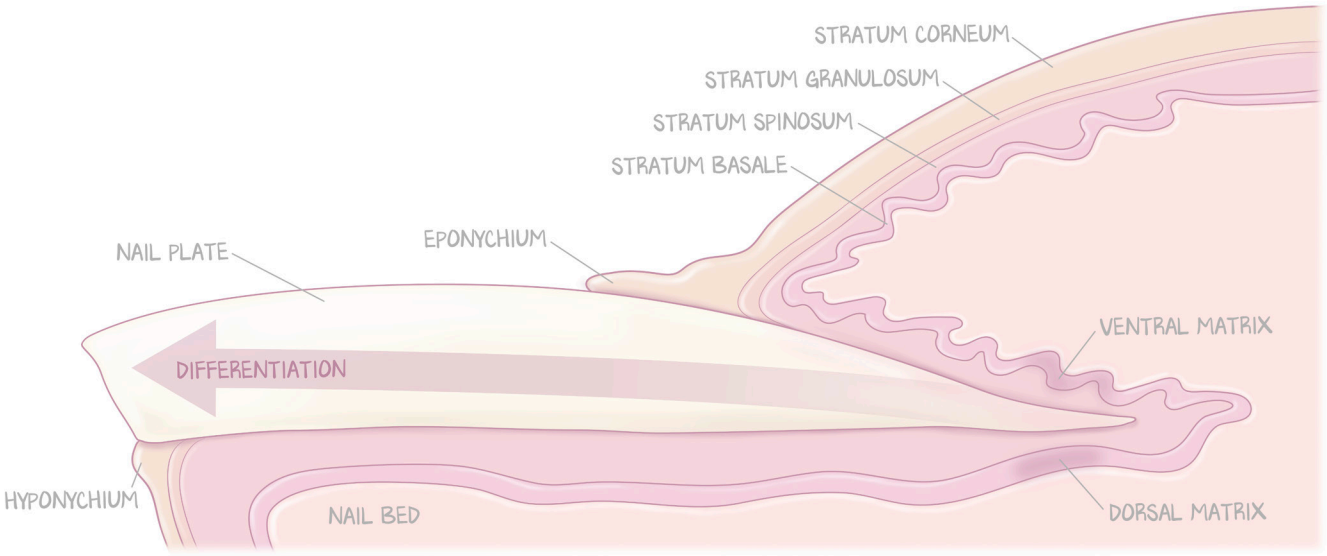

Figure 7.11: Nail Root
Nails are just another appendage of the epidermis. Keratinocytes replicate and turn into corneocytes. The nail grows out from an invagination of epidermis, the nail root. Both the ventral matrix and dorsal matrix act as stem cells. The nail grows out over epidermis. Like a hair follicle, the epidermis in contact with the growing appendage does not have a granulosum nor corneum. At the change from nail-covered epidermis to skin-covered epidermis is a slight overgrwoth of corneum—the eponychium and hyponychium.

The proximal portion of the nail plate is called the **lunula**. It is a white crescent. It is white because the underlying epithelium is thicker here, so the color of the dermis does not show through. The keratinocytes here are also making keratin and have nuclei. Once they eject their nuclei and become corneocytes, they are more translucent. The pink color of the nail is a product of the blood vessels and dermis below the translucent corneocytes.

Onychomycosis is a fungal infection of the nail. To infect the nail, the fungus must have gotten to the nail fold. Fungal cells will subsist in the corneocyte layer, between the corneocytes. The reason topical antifungals don't work on nail infections is because the topical treatment can't get to the matrix—there is nail in the way as well as two layers of dermis / epidermis. And since the nail grows out, not up, fungal treatment needs to be for 90 days, enough time for the entire nail plate with fungus in it to grow and be cut off by the person. Once in treatment, new nail won't have any fungus. If treatment is stopped and there is still fungus in the nail plate, the fungus can reinfect the nail bed, which will start the process all over again.

Acne	Follicles hyperkeratinize, sebaceous glands produce too much sebum *P. acnes* eats sebum, converts to fatty acids Noninflammatory blackheads (open comedones) and whiteheads (closed comedones) Inflammatory pustules or papules
Rosacea	Erythema, telangiectasias, papules, Looks like acne at first glance, but is acute reaction to stressor, not chronic hormones

Table 7.1